UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Office of Prevention, Pesticides
and
Toxic Substances

MEMORANDUM

January 16, 2002

TXR #: 0050395

SUBJECT: **MOLINATE** - Submission by California Rice Commission To Stephen Johnson

TO: Wilhelmena Livingston
Reregistration Branch, SRRD (7508W)

FROM: Linda L. Taylor, Ph.D.
Reregistration Branch I
Health Effects Division (7509C)

THRU: Whang Phang, Ph.D.
Branch Senior Scientist, Reregistration Branch I
Health Effects Division (7509C)

Submitter:	California Rice Commission
Molinate Registrant:	Syngenta Crop Protection, formerly Zeneca
Chemical:	S-ethyl hexahydro-1H-azepine-1-carbothioate
Synonym:	Molinate, Ordram
Caswell No.:	444
PC Code:	041402
DP Barcode:	D277831
Submission:	S603275
Action Requested:	Review.

The California Rice Commission [CRC] submitted to Stephen Johnson [FAX memo dated September 4, 2001] copies of three articles and a Preliminary Draft. The citations of these articles are as follows:

(1) Jewell, W. T. And Miller, M. G. (1998). Identification of a Carboxylesterase as the Major Protein Bound by Molinate. Toxicology and Applied Pharmacology 149, 226-234;
(2) Jewell, W. T.; Hess, R. A.; and Miller, M. G. (1998). Testicular Toxicity of Molinate in the Rat: Metabolic Activation *via* Sulfoxidation. Toxicology and Applied Pharmacology, 149, 159-166;

(3) a pre-publication article by Jewell, W. T. And Miller, M. G. (Not dated). Comparison of Human and Rat Metabolism of Molinate in Liver Microsomes and Slices;

All of these articles were submitted to the Agency previously by the Registrant, Zeneca [now Syngenta]. It is to be noted that these same three articles, along with numerous others, were included as part of the data package presented to the HED Mechanism of Toxicity Assessment Review Committee on **January 13, 2000** [HED Document No. 014033]. Additionally, these same three articles were submitted to the Agency in March, 2001 by CRC [DB Barcode D274266/Submission S595817].

Also submitted was a Preliminary Draft (no date): Is Molinate A Male Reproductive Toxicant in Man? [no author listed; presumably Dr. Marion Miller], which states at the end that this "research is becoming increasingly complex and in need of substantive levels of funding. Therefore, to continue to support the work, I intend to apply to EPA in response to a recent RFA asking for proposals that emphasize mechanism based risk assessment." According to the annual report [Comprehensive Research on Rice, dated January to December, 1999], this research has been funded previously by CRC [DB Barcode D274266/Submission S595817]. Although this article is marked as a Preliminary Draft and: **Do Not Circulate or Cite**, the CRC submitted the draft to the Agency for consideration. There is a MAJOR discrepancy between what is stated in this submission and what the Registrant asserts regarding LDL and rat steroidogenesis. At the bottom of the second page under the heading **"If there are differences in the source of cholesterol from different organs are there differences between species?"**, it states that "for the rat Leydig cells only LDL will support steroidogenesis except under extreme conditions (Quinn et al., 1981)." Syngenta's position is that the rat uses HDL almost exclusively in testosterone synthesis, whereas humans utilize LDL. The researcher [presumably Dr. Marion Miller] also indicates that data to address the possibility that the source of cholesterol is different for the human *vs* the rat Leydig cell will not be available until 2002. During a teleconference with the researcher on December 12, 2001, Dr. Miller indicated that the literature on this point is "murky", not definitive.

It should be noted also that in another CRC submission [DP Barcode D274266; S595817], the annual report of Dr. Miller's research from 2000 for the project entitled "A Metabolic Explanation for Species Differences in Susceptibility to Male Reproductive Toxicity" indicates that it is "possible that mechanism(s) other than inhibition of esterase activity may play a role in the decreased testosterone production seen after molinate sulfoxide." It is to be noted that the inhibition of the esterase is one of the main points in the hypothesis being proposed by the Registrant to support the "rodent-specific" reproductive effect [i.e., inhibition of the cholesterol esterase is proposed to inhibit cholesterol ester hydrolysis, resulting in a decrease in cholesterol for testosterone biosynthesis]. The research results reported in the 2000 annual report suggest that the esterase inhibition may not be directly related to decreased testosterone synthesis. In support of this latter assessment, it is to be noted that the organophosphate tricresyl phosphate [TCP] displays the same target organ toxicity as Molinate, in that it has been shown to inhibit neutral cholesterol esterase and displays an identical morphological effect in the adrenal gland, ovary, and testis of the rat. However, the Leydig cells maintained the ability to produce and secrete testosterone following TCP exposure, unlike Molinate, which inhibits testosterone biosynthesis.

The current submission by CRC does not provide any new data/information that would lead HED to alter its assessment of Molinate with respect to the issue of reproductive toxicity; in fact, the submission lends support to the HED position.